**Scenarios our method doesn't work**

1. when d3 is very close to the maximum allowable threshold for toxicity, our method tend not to select d3 as the optimal dose, k>=2 and k=3 both do not work.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | K=0  (toxicity) | K=1  (no/little efficacy) | K=2  (median efficacy) | K=3  (high efficacy) | CM |
| d1 | 0.15 | 0.6357 | 0.17 | 0.0425 | 1.10 |
| d2 | 0.3 | 0.42 | 0.21 | 0.07 | 1.05 |
| d3 | 0.45 | 0.0275 | 0.11 | 0.4125 | 1.48 |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| N=48 | recommendation for d1 | recommendation for d2 | recommendation for d3 | work |
| k>=2 | 0.3035 | 0.4841 | 0.2124 | no |
| k=3 | 0.2198 | 0.4194 | 0.3608 | no |

1. when each dose has same efficacy but different toxicity, k>=2 and k=3 both do not work.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | K=0  (toxicity) | K=1  (no/little efficacy) | K=2  (median efficacy) | K=3  (high efficacy) | CM |
| d1 | 0.1 | 0.5 | 0.2 | 0.2 | 1.5 |
| d2 | 0.2 | 0.4 | 0.2 | 0.2 | 1.4 |
| d3 | 0.3 | 0.3 | 0.2 | 0.2 | 1.3 |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| N=48 | recommendation for d1 | recommendation for d2 | recommendation for d3 | work |
| k>=2 | 0.1976 | 0.4217 | 0.3807 | no |
| k=3 | 0.1194 | 0.3200 | 0.5606 | no |

1. k=3 works, k>=2 doesn't work

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | K=0  (toxicity) | K=1  (no/little efficacy) | K=2  (median efficacy) | K=3  (high efficacy) | CM |
| d1 | 0.1 | 0.72 | 0.09 | 0.09 | 1.17 |
| d2 | 0.2 | 0.32 | 0.24 | 0.24 | 1.52 |
| d3 | 0.3 | 0.07 | 0.07 | 0.56 | 1.89 |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| N=48 | recommendation for d1 | recommendation for d2 | recommendation for d3 | work |
| k>=2 | 0.1179 | 0.4646 | 0.4175 | no |
| k=3 | 0.1117 | 0.2515 | 0.6368 | yes |

It seems this is caused by the same reason as (b): when k>=2, the success probability of dose 2 and 3 are close (0.48 and 0.63).

if we make the success probability of dose 2 and 3 closer, k>=2 still doesn't work:

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | K=0  (toxicity) | K=1  (no/little efficacy) | K=2  (median efficacy) | K=3  (high efficacy) | CM |
| d1 | 0.1 | 0.72 | 0.09 | 0.09 | 1.17 |
| d2 | 0.2 | 0.26 | 0.30 | 0.24 | 1.58 |
| d3 | 0.3 | 0.07 | 0.07 | 0.56 | 1.89 |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| N=48 | recommendation for d1 | recommendation for d2 | recommendation for d3 | work |
| k>=2 | 0.1151 | 0.5815 | 0.3034 | no |

if we make the success probability of dose 2 and 3 more different, k>=2 works:

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | K=0  (toxicity) | K=1  (no/little efficacy) | K=2  (median efficacy) | K=3  (high efficacy) | CM |
| d1 | 0.1 | 0.72 | 0.09 | 0.09 | 1.17 |
| d2 | 0.2 | 0.4 | 0.16 | 0.24 | 1.44 |
| d3 | 0.3 | 0.07 | 0.07 | 0.56 | 1.89 |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| N=48 | recommendation for d1 | recommendation for d2 | recommendation for d3 | work |
| k>=2 | 0.1127 | 0.3497 | 0.5376 | yes |

1. k>=2 works but k=3 doesn't work

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | K=0  (toxicity) | K=1  (no/little efficacy) | K=2  (median efficacy) | K=3  (high efficacy) | CM |
| d1 | 0.1 | 0.72 | 0.09 | 0.09 | 1.17 |
| d2 | 0.2 | 0.35 | 0.05 | 0.4 | 1.65 |
| d3 | 0.3 | 0.05 | 0.25 | 0.4 | 1.75 |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| N=48 | recommendation for d1 | recommendation for d2 | recommendation for d3 | work |
| k>=2 | 0.1135 | 0.4219 | 0.4646 | yes |
| k=3 | 0.1140 | 0.4886 | 0.3974 | no |

**Summary**

When the success probability is close and toxicity probability has big difference, our method tend to make mistakes.

When the toxicity probability is close to the maximum allowable toxicity, our method tend to make msitakes.

May 22, 2020

Several points.

1. The key to our approach is described in Xue et al p 629

“Our dose escalation algorithm is based on looking for a dose q such that, π\_q3 = π\_q1. Because π\_q3 – π\_q1 is monotone with dose, it is much easier to solve the equation, π­\_q3 – π\_q1 = 0, than maximize the probability of response and no toxicity as a function of dose (Ivanova 2003).”

The problem is that for some scenarios (like those you identified in this file) the solution of equation π­\_q3 – π\_q1 = 0 does not coincide with the maximum of the probability/utility that we want to maximize. Hopefully that are close.

You don’t need to run simulations to see if our method will work, you can just compute the last two columns. The number is bold is the dose that will be selected by our method because it is the closes to 0

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | K=0  (toxicity) | K=1  (no/little efficacy) | K=2  (median efficacy) | K=3  (high efficacy) | CM | K=3 method  π\_tox – π\_3 | K≥2 method π\_tox – π\_2 – π\_3 |
| d1 | 0.1 | 0.5 | 0.2 | 0.2 | 1.5 | -0.1 | -0.3 |
| d2 | 0.2 | 0.4 | 0.2 | 0.2 | 1.4 | **0** | -0.2 |
| d3 | 0.3 | 0.3 | 0.2 | 0.2 | 1.3 | .1 | **-0.1** |

1. A general approach to constructing a dose-finding designs to find the dose such that π­\_q3 – π\_q1 = 0, is to repeat the dose when we are close to 0 (not necessarily 0), otherwise decrease or increase. See my lecture notes pp 38-56.The first design I asked you to run should be similar to the one described on p 46-47
2. Since our method might not pick the dose where the maximum is, we can “correct” it when we come up with the final recommendation of the dose. We can look at the data we collected and select the dose that maximized the utility.